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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,527	06/14/2002	Dirk Johannes Schaefer	0273-0004	4394

73730 7590 12/31/2008

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EXAMINER	
BARNHART, LORA ELIZABETH	

ART UNIT	PAPER NUMBER
1651	

MAIL DATE	DELIVERY MODE
12/31/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/009,527	SCHAEFER ET AL.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-39 and 41-68* is/are pending in the application.

4a) Of the above claim(s) *45-66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-39,41-44,67 and 68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments

Applicant's amendments filed 10/14/08 to claims 36 and 68 have been entered. No claims have been cancelled or added. Claims 36-39 and 41-68 remain pending in the current application, of which claims 36-39, 41-44, 67, and 68 are being considered on their merits. Claims 45-66 remain withdrawn from consideration at this time. References not included with this Office action can be found in a prior action. Any rejections or objections of record not particularly addressed below are withdrawn in light of the claim amendments and applicant's comments.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 36-39, 41-44, 67, and 68 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 36 is drawn to a composition that comprises a "joint side consisting essentially of cultured chondrocytes and/or chondroblasts and cartilaginous substances secreted by the chondrocytes" and an "anchor side consisting essentially of cultured osteoblasts and/or osteocytes and bone substances secreted by the osteocytes" that is produced by an 8-step method. However, none of these steps allow for the addition of chondroblasts to the matrix. It is not clear how these necessary (the matrices) and optional (the blast cells) relate to the overall structure of the composition. The steps in

the product-by-process limitations do not appear to make the product as recited in the preamble. Clarification is required.

Applicant alleges, in relevant part, that chondroblasts give rise to chondrocytes (Reply, page 9, paragraph 6). The arguments have been fully considered, but they are not persuasive. Chondroblasts give rise to chondrocytes, not vice versa. The product-by-process steps do not include a step in which chondroblasts are added to the matrix; therefore, the product-by-process limitations do not produce the embodiment in which the composition contains chondroblasts. Chondrocytes cannot differentiate backward to yield chondroblasts.

Because claims 37-39, 41-44, 67, and 68 depend from indefinite claim 36 and do not clarify this point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 36, 38, 41, 42, 44, 67, and 68 are/remain rejected under 35 U.S.C. 103(a) as being unpatentable over Itay (1991, U.S. Patent 5,053,050) taken in view of Mikos (1996, U.S. Patent 5,522,895), Rosenthal et al. (1995, U.S. Patent 5,466,462), and Jakob et al. (WO 99/21497; and German-to-English translation). Regarding Jakob et al., the page and paragraph numbers in this rejection refer to the English translation, which was made of record 10/24/05.

Itay teaches a composition produced *in vitro* that comprises a biocompatible carrier material (*e.g.* a fibrin matrix) and chondrocytes that have been expanded and enriched in culture medium; the composition may be implanted into defective bones (Examples 1-3 and The Process). The composition of Itay can be produced in any shape, including cylindrical shapes (column 4, line 68) and the particular shape of the damaged area (column 5, lines 3-4), and in any size (Example 3). Because the composition of Itay comprises a fibrin matrix, Itay teaches fibrin adhesion.

Itay does not teach an *in vitro* composition comprising both cultured cartilage cells and cultured bone cells, said composition comprising cartilage cells on one face thereof and bone cells on the opposing face.

Mikos teaches seeding osteoblasts in growth medium onto a biodegradable polymer (column 4, lines 23-29), allowing the suspension to wick into the polymer foam (lines 29-33), and culturing the cells on the polymer to allow them to attach to the foam

(lines 35-55). Mikos teaches that the culturing step allows the osteoblasts to secrete their own extracellular matrix, facilitating cell attachment and gradually eliminating the need for the polymer foam (column 4, lines 46-51). Mikos teaches that biodegradable polymers that form fibers are known in the art and include polyglycolic acid (column 3, lines 30-47). The composition of Mikos may take any desired anatomical shape according to the mold used to shape the polymer (column 3, lines 48-62).

Rosenthal et al. teach that fibrin and polyglycolic acid are functional equivalents in the tissue engineering and wound healing arts (column 1, lines 15-23).

Jakob et al. teach a composition comprising both a bone side and a cartilage side; the composition of Jakob et al. is a column of tissue that has been removed from a donor site at the articular face of a bone (page 2, paragraph 3; Figures 1, 5-7, 9, and 10). Jakob et al. also teach a composition comprising cartilage cells cultured *in vitro* on bone-replacement material (page 5, paragraph 3; page 16, paragraph 3; Figures 11 and 12). The composition of Jakob et al. may have a circular cross-section (page 11, paragraph 4; page 12, paragraph 4; and Figures 13-16) or may have any shape (page 15, paragraph 3).

Claim 36 is a product-by-process claim; claims 37-39, 41-44, 67, and 68 depend from said claims. M.P.E.P. § 2113 reads, "Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps." Applicant is referred to previous Office actions and M.P.E.P. § 2113 for a detailed discussion of product-by-process limitations. In this case, claim 36 requires culturing osteoblasts and chondrocytes separately, then populating one piece of carrier material with the former

and a second piece of carrier material with the latter and connecting the two pieces of material together. There is no evidence on the record to indicate that the product made by such steps would be materially different from one made by, e.g., seeding chondrocytes on one end of a single piece of carrier material and osteoblasts on the other end, or by isolating a portion of the articular face of a bone as taught by Jakob. Such evidence is required to overcome this rejection.

It is noted that claim 36 recites "consisting essentially of." Applicant is referred to previous Office actions and M.P.E.P. § 2111.03 for a detailed discussion of this transitional phrase as it pertains to the claims.

A person of ordinary skill in the art would have had a reasonable expectation of success in combining the *in vitro* cartilage construct of Itay and the *in vitro* bone construct of Mikos because Rosenthal et al. teach that the biodegradable polymers on which each construct is based are functional equivalents for each other; therefore, the cartilage construct of Itay could be modified to include bone cells on one side, and the bone construct of Mikos could be modified to include cartilage cells on one side. The skilled artisan would have been motivated to combine the teachings of Itay and Mikos because Jakob et al. teach that compositions that have bone tissue on one side and cartilage tissue on the opposite side provide efficient repair of defects on the articular face of bone joints (page 15, paragraph 2, *inter alia*).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the *in vitro* bone construct of Mikos and the *in vitro* cartilage construct of Itay to yield a composition comprising cultured cartilage on

one side and cultured bone on the opposite side because Jakob et al. teach that compositions so configured may be implanted into the articular portions of bones to effectively treat defects.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

In response to the section 103 rejections made in the 5/14/08 Office action, applicant supplies arguments that are almost completely identical to those provided in the 3/12/08 reply (compare instant reply, pages 11-14, with 3/12/08 reply, pages 10-12). These comments have been considered as they pertain to the instant claims, and they are unpersuasive for the same reasons as those set forth in the 5/14/08 Office action (refer to pages 11-13 of that action).

The only exception to the verbatim recitation of the 3/12/08 comments is a single sentence at the fifth paragraph of page 12 of the instant reply: "Applicants believe that if the Examiner would advert her mind to the pages in the Specification where the nature of the interlocking area had been reduced to writing or the figures where it had been reduced to drawings Applicants believe that it would be clear that connecting members are structured in an interdigitating fashion configured to ensure firm connectedness of the two sides." These arguments have been fully considered, but they are not persuasive. It is noted that the features upon which applicant relies are not recited in the rejected claim(s). **Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims.** See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The prosecution in this case

has been extensive, during which applicant has frequently urged that limitations from the specification be incorporated into the claims. Such arguments are and will continue to be unpersuasive. The drawings to which applicants refer do not include reference to an "interlocking zone," only a "crosslinking" in Figure 1f. **If the interlocking zone possesses some physical or structural properties that are essential to the patentability of the claimed composition, the claims should be so limited.** Currently, all that is required is that the anchor side and joint side be interlocked in some manner with each other, as is the case in natural bone/cartilage constructs. The **claims** are simply not distinguished over the cited art.

Claim 37 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Itay, Mikos, Rosenthal et al., and Jakob et al. as applied to claims 36, 38, 41, 42, 44, 67, and 68 above, and further in view of Goldstein et al. (1999, U.S. Patent 5,962,427) and Vacanti et al. (1998, U.S. Patent 5,804,178).

The teachings of Itay, Mikos, Rosenthal et al., and Jakob et al. are relied upon as above. Furthermore, Itay teaches that the *in vitro* cartilage composition may include progenitor cells of mesenchymal origin, bone marrow stromal cells, or any undifferentiated mesenchymal cells (column 3, lines 35-46) and may include additional active agents including serum (column 3, lines 47-52).

Itay, Mikos, Rosenthal et al., and Jakob et al. do not teach or suggest including a growth factor that promotes angiogenesis or including endothelial cells or their progenitors in the composition.

Goldstein et al. teach that including DNA encoding vascular endothelial growth factor (VEGF) in an implanted biocompatible matrix promotes angiogenesis at the implant site by transfecting nearby cells (column 2, lines 21-36; column 14, lines 13-45; and column 24, lines 7-29). The matrix of Goldstein et al. may be any biodegradable matrix (column 11, line 19, through column 14, line 4), including PGA (column 12, line 35). Goldstein et al. also teach administering recombinant VEGF protein (column 2, line 42, through column 3, line 31).

Vacanti et al. teach implanting endothelial cells in a biodegradable matrix such as PGA (Abstract; column 3, lines 5-41; column 4, lines 52-57; column 5, lines 49-50).

A person of ordinary skill in the art would have had a reasonable expectation of success in including either pro-angiogenic growth factors (such as VEGF) or cells carrying cDNAs therefor or endothelial cells *per se* (which are required structural components of blood vessels) in the composition of Itay in view of Mikos, Rosenthal et al., and Jakob et al. because Itay suggests including additional cell types and additional active agents and because Goldstein et al. and Vacanti et al. teach that VEGF protein, VEGF cDNA, cells transfected with VEGF cDNA, and endothelial cells may be implanted using a biocompatible matrix equivalent to those employed by Itay and Mikos. The skilled artisan would have been motivated to include endothelial cells and/or pro-angiogenic growth factors for the expected benefit of increasing the degree of vessel formation around the implant after it has been placed into a recipient, thus improving the implant's ability to incorporate into the recipient's body.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to include the pro-angiogenic factors of Goldstein et al. or the endothelial cells of Vacanti et al. in the composition of Itay taken in view of Mikos, Rosenthal et al., and Jakob et al. because Goldstein et al. and Vacanti et al. teach that these components improve angiogenesis upon implantation of such a composition, thus increasing the chance that the composition successfully engrafts in a patient.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

In response to the section 103 rejections made in the 5/14/08 Office action, applicant supplies arguments that are almost completely identical to those provided in the 3/12/08 reply (compare instant reply, pages 14-15, with 3/12/08 reply, pages 13-14). These comments have been considered as they pertain to the instant claims, and they are unpersuasive for the same reasons as those set forth in the 5/14/08 Office action (refer to pages 15-16 of that action).

No claims are allowed. No claims are free of the art.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is (571)272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart/
Primary Examiner, Art Unit 1651